REMARKS

Claims Free of the Art

Applicants gratefully acknowledge the determination by the Patent Office that Claims 61-63, 71-74, and 76-87 are free of the prior art.

Claim Amendments

Support for the above claim amendments can be found through out the specification and claims as originally filed. Specifically, support for the limitation that the "cells of the tumor are modified *in vivo* by local administration of a nucleic acid molecule encoding B7-2" is found on at least on page 19, lines 5-6. Support for the phrase "viral vectors", "retroviral vectors", "adenoviral vectors" and "adeno-associated viral vectors" can be found at least on page 18, lines 32-36. No new matter has been added.

Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely in order to expedite prosecution. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Objections to the Claims

Claims 78 and 87 have been objected to because of informalities. In response, these informalities have been corrected by the above amendments to the claims. Applicants respectfully request that the objections to Claims 78 and 87 be withdrawn.

Rejection of Claims 61-62, 71-74 and 76-87 Under 35 USC 112, First Paragraph

Claims 61-62, 71-74 and 76-87 have been rejected under 35 USC 112, first paragraph as being drawn to an invention which is not enabled by the specification. More specifically the Examiner states:

> due to lack of direction, guidance provided by the specification ... the unpredictability of the gene therapy art, and the breadth of the claims, it would have required undue experimentation without a predictable degree of success for one skilled in the art to make and use the instant broadly claimed invention.

It is the position of the Examiner that the nature of the elected invention falls within the realm of *in vivo* gene therapy and that at the effective filing date of the present application, the art of gene therapy was immature and highly unpredictable. In support of this assertion the Examiner cites statements made in the disclosure of Marshall et al. (Science 269: 1050-1055 (1995)), Dang et al., (Clin. Cancer Res. 5: 471-474 (1999)), Miller et al. (FASEB 9: 190-199 (1995)), Deonarain (Exp. Opin. Ther. Patents 8: 53-69 (1998)), Verma et al., (Nature 389: 239-242 (1997)) and Wivel et al. (Hematol. Onco. Clin. North Am. 12: 483-501 (1998)), Eck et al., (Gene-based therapy (1996)), and Branch et al., (TIBS) 23: 45-50 (1998)).

This rejection is respectfully traversed. The fact that certain aspects of a field may be in their infancy does not preclude the existence of enabled inventions in that field. Aspects of the field of gene therapy which are highly unpredictable relate to prolonged gene expression and efficient gene delivery to target cells. Such aspects of gene therapy are not as critical to the present invention as to the type of gene therapy discussed in Marshall et al., Dang et al., Miller et al., Deonarain, Verma et al. Wivel et al., and Eck et al. The cited disclosures specifically refer to applications of gene therapy in which prolonged and widespread expression of an introduced gene in an individual is necessary. This is not the case with the present invention, in which neither prolonged nor widespread expression of the introduced B7-1 encoding nucleic acid molecule is necessary. Modification of tumor cells to express B7-1 is expected to be of therapeutic benefit to a subject even if expression of the introduced gene is short lived and expressed only by a subset of tumor cells within the population. The specification repeatedly states that the anti-tumor immune response induced by the modified tumor cells is effective against both

the modified tumor cells and unmodified tumor cells which do not express a costimulatory molecule (see page 7, line 32-37, page 19, line 14-20, page, 22, line 35-38, page 23, line 13-15). A working example showing this is presented in Example 2.

The disclosure of Marshall is specifically cited as disclosing that the field is at an early stage of development and lacks conclusive evidence that genetic treatment has produced therapeutic benefit. However, Applicants point out that the disclosure of Marshall primarily focuses on gene replacement therapy to treat genetic disorders and assumes that therapeutic results may only be achieved by sustained high expression of the transfected gene. This is also the assumption Marshall makes with respect to cancer therapy stating "most protocols aim to induce specific cells, such as cancer cells or cells infected by HIV, to produce proteins that would make them vulnerable to attack by the immune system." Because of this assumption, the comments of Marshall do not apply to the present invention since Marshall does not take into consideration Applicants' findings that modification of a small portion of the tumor cells in an individual is sufficient to generate an immune response to all tumor cells, both modified and unmodified. Thus aspects of the disclosure of Marshall cited in the rejection are not relevant with respect to the claimed invention. Although Applicants acknowledge that certain aspects of the field of gene therapy may be at an early stage of development, this does not preclude the use of gene therapy for applications in which the indicated obstacles do not apply. Moreover, Marshall teaches that there are applications where gene therapy is expected to be useful (page 1055, column 1, first paragraph).

The disclosure of Dang et al. is cited as evidence that the field of gene delivery and the art of gene therapy was still immature and unpredictable at the effective filing date of the invention. The Examiner maintains that the obstacles blocking gene therapy from achieving therapeutic effects could not have been overcome with routine experimentation. In Dang et al., these obstacles are identified as suboptimal vectors, host immunological responses to the vectors and the lack of long term stable expression,

which result in inefficient gene delivery to target tissues (last paragraph of page 474). Applicants submit that the host immunological responses and lack of long term stable expression are not significant drawbacks in reference to the present invention, and the vectors determined by Dang et al. to be suboptimal are indeed sufficient to produce therapeutic results. Thus, these aspects of the disclosure of Dang et al., are not relevant to the claimed invention. In fact, Dang et al. cite evidence which supports Applicants' assertion that an immune response mounted to modified tumor cells can also be useful in targeting non-modified tumor cells (see page 473, second column, lines 9-17, and lines 33-45).

The disclosures of Miller et al., Deonarain, Verma et al., Wivel et al., and Eck et al. are cited in support of the assertion by the Examiner, regarding Claims 73-74 and 76-87, that:

> the instant specification is not enabled for the broadly claimed invention because it fails to provide sufficient guidance demonstrating that any therapeutic effects has [sic] been achieved for treating a patient having a tumor by delivering to the patient a nucleic acid molecules [sic] encoding B7-2 molecule or in combinations with other nucleic acid molecules as claimed. The mere exemplification (Example 5) showing that no tumor growth was observed upon intradermal or subdermal implantation of J558 plasmacytoma cells transfected *in vitro* with an expression vector containing cDNA encoding either mouse B7-2 or B7-1 molecule in syngeneic Balb/c mice is not deemed to have a reasonable correlation with the entire scope of the instant elected invention.

In response to the Examiner's position that the findings made in the experiments detailed in Example 5 do not have a reasonable correlation with the scope of the claims, Applicants respectfully point out the data presented in Example 2. In this Example, immunization of mice with sarcoma cells transfected to express B7 provides protective immunity to subsequent challenges with sarcoma cells which do not express B7. This indicates that expression of a B7 molecule is not needed on the tumor targets once the appropriate effector T cell populations are generated. These findings are directly applicable to expression of the other B7 molecules (e.g., B7-2) in tumor cells, in light of

the data presented in Example 5 regarding the ability of B7-2 expression to confer immunogenicity to tumor cells.

The Examiner further states, regarding the rejection of Claims 73-74 and 76-87, that:

> at the effective filing date of the present application, *in vivo* effector targeting to desired cells, tissues or organs, for this instance tumor cells, continues to be unpredictable and inefficient.

Regarding the unpredictability and inefficient targeting of effector to desired cells, Miller et al. is cited as disclosing that :

> for the long term success as well as the widespread applicability of human gene therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems.

Again, long term success and widespread applicability of gene therapy are not required for the enablement of the present invention. Applicants respectfully point out that statements made in Miller et al. do not take the present findings into consideration. This is evident from Miller et al.'s statements that "cancer gene therapy usually involves the targeting (of a corrective gene) of all of a diffusely spread population of cells" (emphasis added). As explained above, this is not the case for the present invention. As taught in the specification, therapeutic results are achieved by gene delivery to only a fraction of all tumor cells in a patient. Thus, these aspects of the disclosure of Miller et al., are not relevant to the present claims. Furthermore, the teachings of Miller et al. support the enablement of the present invention stating that "technology now exists to incorporate specific targeting features into most of the currently available delivery systems" (page 190, column 2, lines 2-4).

The disclosure of Deonarain is cited by the Examiner as disclosing that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time." In response, Applicants reiterate their comments made above, i.e., because prolonged expression is not required to achieve a therapeutic effect using the claimed methods, this is not an obstacle and thus does not preclude enablement of the present invention. Further, in reference to currently available gene delivery methods, Deonarain makes statements which support Applicants' assertion of an enabling disclosure, stating that "under optimal conditions, enough gene product may be produced to give therapeutic benefit (e.g., suppress a phenotype or destroy a tumour) (page 65, column 1, first two sentences of the last paragraph).

The disclosure of Verma et al. is cited as teaching that, at the time of the claimed invention, resolution to vector targeting had not been achieved in the art, and that the immune system inhibits efficient targeting of viral vector to preclude efficient expression, and also that the search for appropriate enhancer-promoter sequences which improve expression is a case of trial and error for a given cell type. Applicants reiterate their statements made above regarding the lack of necessity of long term expression or widespread delivery to target tumor cells. Thus, the disclosure of Verma et al. is not relevant to the present invention.

The disclosure of Wivel et al. is cited in support of the Examiner's assertions that there are several factors known to limit effective gene therapy, including the lack of an optimal vector and the lack of stable transgene expression in vivo. Wivel et al. is specifically quoted as stating:

> One of the major challenges still confronting the field is the design of more efficient vectors. The gene delivery systems being used today will undoubtedly be seen as crude when compared with future developments.

In response, Applicants point out that these statements are immaterial to the present invention. As stated previously, the present invention does not require long term expression or delivery of the gene to all tumor cells in a population. In addition, Applicants note that the nature of progress is such that early work is almost always seen as crude when compared with future developments, but this does not preclude the existence of patentable inventions within a field at any given time. Furthermore, the teachings of Wivel et al. support Applicants assertions of enablement of the present invention, disclosing:

> Although formidable problems surround the immunologic responses to adenovial vectors, nothing precludes their use in clinical situations in which short-term gene expression is all that is necessary and in which vector re-administration is not mandatory (page 489, first sentence, last paragraph).

The disclosure of Eck et al. is cited as teaching that the level of mRNA produced, the stability of the protein produced, the protein's proper compartmentalization within the cell or its secretory fate differ dramatically based on which protein is being produced, and therefore the desirable therapeutic effects sought to achieve. In response, Applicants respectfully point to their demonstration of the production of B7-2 protein from exogenous nucleic acid in transfected tumor cells (in Example 5 of the present specification), and also their demonstration of the production of B7 protein from tumor cells transfected with a nucleic acid molecule encoding B7 (see Examples 1 and 2). Furthermore, the expression of exogenous MHC Classs II α and β chains, as well as β-2 microglobulin has been demonstrated in the art, thus demonstrating that the concerns noted by Eck et al. are not relevant to the present invention.

Regarding Claims 81 and 82, the Examiner states that the specification fails to provide guidance showing that any effective antisense nucleic acid molecule could be obtained inhibiting the expression of the invariant chain in tumor cells *in vivo* to achieve the desired therapeutic effects, citing Branch (TIBS 23: 45-50 (1998)) as evidence of unwanted non-antisense effects known to be associated with the antisense strategy. In

response, Applicants point out that such a nucleic acid molecule which is antisense to a coding or regulatory region of the Ii gene, has been previously described. Koch, N., et al., *EMBO J.* 6, 1677-1683, (1987) (as stated in the specification on page 17, line 5-8).

In summary, despite the limitations in some areas of the field of gene therapy at the time of the present invention, the present invention can be made and used by one of ordinary skill in the art through no more than routine experimentation, since evidence suggests that the present invention does not require long term expression, seen to be an obstacle in other forms of gene therapy. Applicants further note that dependent claims 63 and 88 and the claims that depend therefrom specify a specific means of introduction of the nucleic acid molecule into a cell. It is Applicants' position that one of ordinary skill in the art could make and use the invention as claimed using no more than routine experimentation. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection of Claims 61-63, 71-72 Under 35 USC 112, Second Paragraph

Claims 61-63, 71-72 have been rejected under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. More specifically the Examiner indicates that "there is a lack of step(s) linking the step of modifying tumor cells *in vivo* with "treating" recited in the preamble of" Claims 61-63 and 71-72, and requests clarification.

In response, Claim 61 has been amended to more recite that the method for treating a subject with a tumor comprises modifying cells of the tumor *in vivo* to express a T cell costimulatory molecule, B7-2, to thereby treat the subject. It is respectfully submitted that this amendment adequately links the treating step with the modifying step as the term "modifying the cells of the tumor in vivo" clearly represents modification of the tumor cells within the subject.

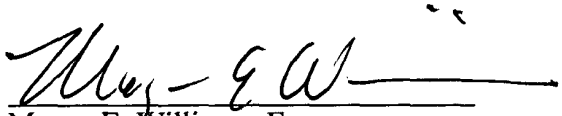
In addition, the Examiner indicates that there is insufficient antecedent basis of the limitation "the nucleic acid" in claim 63. In response, claim 63 has been amended to

instead depend from claim 62, rather than claim 61. Antecedent basis for "the nucleic acid" is provided in claim 62.

SUMMARY

In light of the above amendments and remarks, Applicants respectfully request reconsideration of the subject application. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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APPENDIX A

Version of Amended claims showing changes made:

61. (Amended) A method for treating a subject with a tumor comprising modifying cells of the tumor [cells] *in vivo* to express a T cell costimulatory molecule, B7-2_2 to thereby treat the subject.

62. (Amended) The method of claim 61 wherein cells of the tumor [cells] are modified *in vivo* by delivering to the cells [subject] *in vivo* a nucleic acid molecule encoding B7-2 in a form suitable for expression of B7-2 by the cells.

63. (Amended) The method of claim 62 [61] wherein the nucleic acid molecule is delivered to the cells [subject] *in vivo* by injection of the nucleic acid molecule in an appropriate vehicle into the tumor.

72. (Amended) The method of claim 62, wherein the nucleic acid molecule encoding B7-2 comprises the nucleic sequence shown in SEQ ID NO:1.

78. (Amended) The method of claim 73 wherein the tumor cells are further transfected with at least one nucleic acid molecule encoding at least one MHC class II α chain protein and at least one MHC class II β chain protein in a form suitable for expression of the MHC class II α chain protein(s) and the MHC class II β chain protein(s).

82. (Amended) The method of claim 81 wherein expression of the invariant chain is inhibited in the tumor cells by transfection of the tumor cell with a nucleic acid molecule which is antisense to a regulatory or a coding region of the invariant chain gene.

87. (Amended) A method of increasing the immunogenecity of a tumor cell comprising, modifying the tumor cell to express a B7-2 T cell costimulatory molecule such that the immunogenicity [immunogenecity] of the tumor cell is increased.